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September 24, 1992

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Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

Re: CAP Agreement Identification No. 8ECAP-0110

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") herewith submits the following report pursuant to the terms of the TSCA §8(e) Compliance Audit Program and Union Carbide's CAP Agreement dated August 14, 1991 (8ECAP-0110). This report describes reproductive studies with nine selected chemicals including: ethylene glycol mnonoethyl ether (CASRN 110-80-5), ethylene thiourea (CASRN 96-45-7), ethylene glycol monobutyl ether (CASRN 111-76-2), ethylene glycol monomethyl ether (CASRN 109-86-4), and ethylene glycol monobutyl ether (CASRN 111-76-2).

"Determination of the Reproductive Effects in Mice of Nine Selected Chemicals", Bioassay Systems Corp. (for NIOSH), BSC Project No. 10867, January 7, 1983.

A complete summary of this report is attached.

Previous TSCA Section 8(e) or "FYI" Submission(s) related to this substance are:

(None)

Previous PMN submissions related to this substance are: (None)

bscproj

(2)

This information is submitted in light of EPA's current guidance. Union Carbide does not necessarily agree that this information reasonably supports the conclusion that the subject chemical presents a substantial risk of injury to health or the environment.

In the attached report the term "CONFIDENTIAL" may appear. This precautionary statement was for internal use at the time of issuance of the report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Yours truly,

William C. Kuryla, Ph.D.
Associate Director
Product Safety
(203/794-5230)

WCK/cr
Attachment (3 copies of cover letter, summary, and report)

bscproj

SUMMARY

DETERMINATION OF THE
REPRODUCTIVE EFFECTS IN MICE
OF NINE SELECTED CHEMICALS

NIOSH Contract No. 210-81-6011
Project Officer: Ronald Schuler

Submitted by:

BIOASSAY SYSTEMS CORPORATION
225 Wildwood Avenue
Woburn, Massachusetts 01801

BSC Project No.: 10867

Prepared by:

Kirby N. Smith, DVM
Study Director

Jan. 7, 1983
Date

01/07/83

50-2-58

EGEE

B-6

DETERMINATION OF THE REPRODUCTIVE EFFECTS IN MICE OF NINE SELECTED CHEMICALS

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1. OBJECTIVE

The purpose of this study was to screen for the potential reproductive effects of nine selected NIOSH test substances. These nine chemicals were number coded during the study so that no laboratory or supervisory personnel were aware of their specific identity. Maximum tolerated dose levels were determined, and were then used in subsequent reproductive studies. The maximum tolerated dose (MTD) was initially defined as the highest dose which results in weight reduction during the study period not greater than 10% compared to the controls and which results in no animal mortality. This was changed prior to testing to include criteria of a minimum mortality to be expected in the reproductive phase. Doses were chosen by the Project Officer for the subsequent reproductive studies from the results of the MTD study, available data from the literature, clinical signs, and from other sources.

All chemicals were then assayed for their potential to produce adverse reproductive effects, by utilizing the modified postnatal mouse screening test described by Chernoff and Kavlock (Teratology, 21 (2): 33A, 1980).

2. EXPERIMENTAL DESIGN

2.1 Animals

2.1.1 Test animal

For the maximum tolerated dose studies, a total of five hundred twenty adult, virgin, non-pregnant, specific pathogen free (SPF) CD-1 female mice were used for all nine chemicals. The mice ranged in age from sixty to eighty days and ranged in weight from 25.1 to 35.8 grams, for the MTD Block I study. The mice ranged in age from six to eight weeks of age for MTD Blocks II and III. Weight ranges of mice used were 20.3 to 28.8 g for MTD II, and from 22.6 to 28.4 g for MTD Block III. They were purchased from Charles River Breeding Laboratories, either at Wilmington, MA for MTD I and MTD II (except 20), or Lakeview, NJ (LO4) for MTD III and twenty for MTD II.

For the entire reproductive phase of the study, six hundred adult female timed-pregnant 5-days specific pathogen-free CD-1 mice were used. These mice ranged in age from six to eight weeks old, and ranged in weight from 20.1 g to 36.7 g, 19.5 g to 34.0 g, and 21.5 g to 34.8 g, for Reproductive Blocks I, II, and III respectively. They were purchased from Charles River Breeding Laboratories, Wilmington, MA for Reproductive Blocks I and II, and from Lakeview, NJ for Reproductive Block III.

2.1.2 Identification and randomization procedures

Animals were identified by ear punch code. In addition, the test substance and dose level were identified on the animal cage card.

Block III: Corn Oil (vehicle control)	--
Toluene	735 mg/kg Body weight 1470 2945 5890 8700
2,4-dinitrotoluene (DNT)[b]	310 mg/kg Body weight 525 1250 2500 3500
2,4-diaminotoluene (DAT)	150 mg/kg Body weight 175 200 225 250

For the reproductive studies, doses were chosen based on the results of the MTD experiments. The dose levels chosen (see the Results section) for each chemical are as follows:

Test Substance		Dose Level
Blocks I and II:	Water (Vehicle control)	—
	SS	5 mg/kg
	EtTu	300
	DGME	4000
	EGME	1400
	EGEE	3605
	EGBE	1180
Block III:	Corn Oil (Vehicle control)	--
	TOL	2350
	DNT	390
	DAT	150

[b]The second dose level for DNT should have been 625 mg/kg BW. The actual dose prepared was thus 16% low, due to a chemistry transcription error.

3.2.3 Ethylene glycol monoethyl ether (EGEE)

Statistically, there was no significant difference among the mean body weights of any of the dose groups or control group at any of the weight measurement times ($F < 1$). The mean body weights of all the treated groups were within 10.0% of the control group mean body weights throughout the study (Tables 31 and 32).

Statistical comparison of the body weight changes of treated groups with the control group showed that these changes were similar at each of the three time intervals examined (Table 33).

Mortality for EGEE is summarized in Table 34. One animal administered 3605 mg/kg BW died on the fourth dosing day. This death was not due to gavage error or disease. No animals died during the post-dosing period of observation. There were no deaths in the control group.

Clinical signs of animals in the Maximum Tolerated Dose study of EGEE are shown, compared to controls, in Tables 35 and 36.

Based on the results of the MTD study for this chemical, a dose level of 3605 mg/kg for the Reproductive study was chosen.

TABLE 31

Effect of the administration of Ethylene glycol monoethyl ether (EGEE) on the body weight of female mice[a]

Dose level (mg/kg BW)	Dosing period (days) 1	Dosing period (days) 8	Post-dosing period (days) 4	Post-dosing period (days) 8
Vehicle Control	25.2 ± 1.7 (10)	26.4 ± 2.5 (10)	27.7 ± 2.7 (10)	28.9 ± 2.8 (10)
225	24.9 ± 2.2 (10)	25.5 ± 2.5 (10)	26.7 ± 2.0 (10)	28.0 ± 2.2 (10)
450	25.2 ± 1.3 (10)	25.9 ± 1.4 (10)	27.2 ± 1.6 (10)	28.1 ± 1.4 (10)
900	25.1 ± 1.5 (10)	26.1 ± 1.4 (10)	27.3 ± 1.6 (10)	28.1 ± 1.5 (10)
1800	25.2 ± 1.4 (10)	25.7 ± 1.3 (10)	27.1 ± 1.6 (10)	28.6 ± 1.7 (10)
3605	25.2 ± 0.9 (10)	25.7 ± 0.7 (9)	26.5 ± 0.8 (9)	28.1 ± 1.2 (9)
Statistical Analysis				
One-Way ANOVA	$F^{P}_{5,54}=0.045$	$F^{P}_{5,53}=0.301$	$F^{P}_{5,53}=0.51$	$F^{P}_{5,53}=0.336$
Conclusion[b]	F < 1 N.S.	F < 1 N.S.	F < 1 N.S.	F < 1 N.S.

[a] All values are grams, mean ± S.D.; group size is indicated in parenthesis.

[b] N.S. = Not Significant

TABLE 32

Relative effects of the administration of Ethylene glycol monoethyl ether (EGEE) on the body weights of female mice[a,b]

Compound	Dose Level	Dosing Period 8th day	Post-dosing period 4th day	Post-dosing period 8th day
Ethylene glycol monoethyl ether (EGEE)	225 mg/kg BW	- 3.4 (10)	- 3.6 (10)	- 3.1 (10)
	450 "	- 1.9 (10)	- 1.8 (10)	- 2.8 (10)
	900 "	- 1.1 (10)	- 1.4 (10)	- 2.8 (10)
	1800 "	- 2.7 (10)	- 2.2 (10)	- 1.0 (10)
	3605 "	- 2.7 (9)	- 4.3 (9)	- 2.8 (9)

(a) Percent of relative effect on body weights at three different time intervals after study initiation, as compared to the vehicle control group (=100%) at the same time interval.

(b) This table was prepared using the average body weights shown in Table 31. Results are percent change; test group size is indicated in parenthesis.

TABLE 33

Body weight changes of female mice as compared to the initial weight, at 3 time intervals following administration of Ethylene glycol monoethyl ether (EGEE) (a)

Dose level (mg/kg BW)	Dosing period 8th day	Post-dosing period 4th day	Post-dosing period 8th day
Vehicle Control	1.2 ± 1.6 (10)	2.5 ± 1.6 (10)	3.7 ± 1.7 (10)
225	0.6 ± 1.0 (10)	1.8 ± 0.5 (10)	3.1 ± 1.3 (10)
450	0.7 ± 0.7 (10)	2.0 ± 0.7 (10)	2.9 ± 1.0 (10)
900	0.9 ± 1.1 (10)	2.1 ± 1.3 (10)	3.0 ± 1.2 (10)
1800	0.6 ± 0.9 (10)	1.9 ± 1.1 (10)	3.4 ± 1.4 (10)
3605	0.5 ± 0.9 (9)	1.3 ± 1.0 (9)	2.9 ± 1.1 (9)
Statistical Analysis			
One-Way ANOVA	$F^{P}_{5,53}=0.652$	$F^{P}_{5,53}=1.195$	$F^{P}_{5,53}=0.646$
Conclusion (b)	F < 1 N.S.	P=0.324 N.S.	F < 1 N.S.

(a) All values are grams, mean ± S.D.; group size is indicated in parenthesis.

(b) N.S. = Not Significant

TABLE 34

Mortality Data for Ethylene glycol monoethyl ether (EGEE)

Dose Level(a)	225		450		900		1800		3605	
Number on Test	(10)		(10)		(10)		(10)		(10)	
Cause of Death(b)	Test	Gavage	Test	Gavage	Test	Gavage	Test	Gavage	Test	Gavage
Treatment Day 1										
2										
3										
4									1	
5										
6										
7										
8										
Observation Day 1										
2										
3										
4										
5										
6										
7										
8										
Cumulative Deaths	0		0		0		0		1	

(a) mg/kg Body Weight
(b) Where Test Death = a death attributable to toxicity of the test material
Where Gavage Death = a death attributable to gavage error
There were no deaths in the control group at any time.

TABLE 35

Clinical Observations of Animals During Dosing Period(*)

Test Compound	Dose Level	Day of Treatment 1	2	3	4
Vehicle Control	----	---	---	---	---
Ethylene glycol monoethyl ether (EGEE)	225 mg/kg BW	---	---	---	---
	450 mg/kg	---	---	---	c(10)i(1)
	900 mg/kg	---	---	c(2)	c(9)
	1800 mg/kg	---	---	c(3)	c(10)
	3605 mg/kg	a,f(10)	---	c(1)	a,c,f(9)d,i(1)

Test Compound	Dose Level	Day of Treatment 5	6	7	8
Vehicle Control	----	---	---	---	---
Ethylene glycol monoethyl ether (EGEE)	225 mg/kg BW	a,c(10)	c(2)	---	c,i(1)
	450 mg/kg	a,c(10)	---	c(1)	c,h(1)
	900 mg/kg	c(10)	---	---	---
	1800 mg/kg	c(10)a(4)i(1)	c(5)a,i(1)	c(3)	c(4)h(1)
	3605 mg/kg	a,c,f(9)h(3)i(1)	a,f(9)	a,f(9)c(3)	c(3)

(*) Number of animals affected is indicated in parenthesis.

Code:
a = Lethargy with or without previous activity; b = dyspnea or decreased respiration; c = rough coat; d = death, natural; e = apparent weight loss; f = staggering and/or falling; g = death, gavage error; h = hunched; i = squinted eyes; j = prostrate or moribund; k = piloerection; l = lacrimation; m = muscle control loss; n = bleeding from urogenital region; p = decrease in body temperature.

TABLE 36

Clinical Observations of Animals During the Post-Treatment Period (*)

Test Compound	Dose Level	Animals Per Group	Post-treatment period (days) 1	2	3	4
Vehicle Control	----	10	---	---	---	---
Ethylene glycol monoethyl ether (EGEE)	225 mg/kg BW	10	---	---	---	---
	450 mg/kg	10	---	---	---	---
	900 mg/kg	10	---	---	---	---
	1800 mg/kg	10	c(1)	---	---	---
	3605 mg/kg	9	---	---	---	---

Test Compound	Dose Level	Post-treatment period (days) 5	6	7	8
Vehicle Control	----	---	---	---	---
Ethylene glycol monoethyl ether (EGEE)	225 mg/kg BW	---	---	---	---
	450 mg/kg	---	---	---	---
	900 mg/kg	---	q(1)	q(1)	---
	1800 mg/kg	---	---	---	---
	3605 mg/kg	---	---	---	---

(*) Number of animals affected is indicated in parenthesis.

Code:

c = rough coat; q = left hind leg seems partially paralyzed-holds it up while walking.

4.0 RESULTS OF THE REPRODUCTIVE STUDIES

Results of the reproductive studies and statistical analyses are summarized on Tables 61 to 78.

4.1 Sodium selenite (SS)

Maternal reproductive and litter data, and statistical analysis indicates there were no significant differences between the test and control groups for any of the measures of reproductive toxicity. The change in maternal weights from day 7 to day 18 of gestation is not significant when compared to the vehicle control. It should be noted that for this chemical, due to a technical error in the assignment of the term "day 1" of gestation, many dams gave birth just prior to their being weighed on day 18. However, the statistical analysis is conducted so that this makes no difference in the significance of the results. That is, for maternal weight gain during pregnancy, immediate post-partum maternal weights and their litter weights are added for each animal in both test and control groups, and then compared statistically. Placental weights and fluids were not included for any test or control animal or litter. All other measures are conducted exactly as specified.

4.2 Ethylene thiourea (EtTu)

Significantly fewer live pups per litter were present both 12 hours after birth and 3 days postpartum in mated females tested with this chemical. Other measures of reproductive toxicity were not significantly affected. However, the trend towards greater percentage dead pups per litter within twelve hours of birth may be noted. The same additional comments with regard to the births prior to weighing on day 18 due to inappropriate designation of "day 1" apply to this test as for the previous chemical. The statistics were handled similarly for both test and control groups.

4.3 Diethylene glycol monomethyl ether (DGME)

Five mated female mice of the fifty, which were administered this chemical at the designated tolerated dose, died during the dosing period. At necropsy, none were found to have evidence of gavage error; four were pregnant when they died. Eighteen of the remainder resorbed their litters *in utero*. Nine litters were stillborn. Only five managed to produce viable litters, out of the group mated, yielding a very low reproductive index (0.14). During the subsequent three days another litter died out entirely. The live pups uniformly did more poorly than did the live pups in the control group. Where there was sufficient data to support effective statistical analysis (all measures except number of dead pups within 12 hours), highly statistically significant differences were found between test and control groups for all other measures of reproductive toxicity.

4.4 Ethylene glycol monomethyl ether (EGME)

Seven mated female mice died, of the fifty dosed with this chemical, and only one death could be attributed to gavage error. All 7 were pregnant, and two of these pregnancies were resorbed. Every one of the remaining (30) pregnant mice resorbed their litters *in utero*. There were no viable births, and no litters even carried to term. No statistical manipulations were necessary, therefore, to conclude that this material is highly toxic to the normal reproductive process at all stages except the earliest ones of fertilization and implantation. The reproductive index was 0.00, due to uniform failure of gestational completion, and the deaths of all fetuses *in utero*.

4.5 Ethylene glycol monoethyl ether (EGEE)

Five mated female mice died in the test group (two during the dosing period and three after the dosing period was completed), and three of these five were pregnant. No deaths could be attributed to gavage error. All of the (32) remaining pregnant mice resorbed their litters *in utero*. No viable births occurred, and the reproductive index was 0.00. Due to the highly feto-toxic nature of these effects, to all reproductive phases subsequent to implantation, no statistical analysis is required for its demonstration. The toxic effects of this and the previous chemical on the reproductive process appear similar, by the measures tested in these experiments.

4.6 Ethylene glycol monobutyl ether (EGBE)

Eleven mated female mice dosed with this chemical died; four during the dosing period, and seven after dosing was completed. None of the deaths were due to gavage error. Five of these eleven were pregnant. One of these pregnant mice gave birth and died subsequently. The difference between the test and control groups in the number of viable litters produced is a reflection of both the direct toxicity of the chemical, and also its reproductive effects, i.e., that of causing *in utero* deaths. The difference in the reproductive index is markedly affected by the seven resorbed litters in the test group. No other statistical measures of reproductive toxicity were significantly different between test and control groups. However, the trend toward lower maternal body weight gains during pregnancy and lower maternal body weights at term, may be noted.

4.7 Toluene (TOL)

Only one test animal died during the experiment and there were no statistically significant differences between test and control groups in any of the categories for evaluation of reproductive toxicity. A nonsignificant trend towards lower weight gain in pregnancy may be noted.

TABLE 69. Ethylene glycol monoethyl ether (EGEE): Maternal and Reproductive Data

	Vehicle Control deionized H20	Test dose 3605 mg/kg	Statistical Analysis[c]: Model I ANOVA or chi-square
No. mated mice initially on study	50	50	
No. died on test			
Dosing period	0	2	
Post-dosing	0	3	
Non-pregnant of these	0	2	
No. mice producing viable litters	31	0	
Stillborn litters	0	0	
No. mated mice with totally resorbed litters[a]	1	32	
Total Non-Pregnant	17[d]	15	
Reproductive Index[b]	0.97	0.00	---
Mated animals: Initial body weight (day 7)	28.3 ± 2.5 (50)	28.5 ± 2.5 (50)	N.S.
Maternal BW of animals prior to delivering on day 18	48.6 ± 4.6 (31)	---	---
Change in BW (day 7-18)	19.7 ± 3.7 (31)	---	---
Maternal BW 3 days postpartum (those with viable litters)	33.9 ± 3.9 (31)	---	---

(a) As determined by the sulfide nidation site test.

(b) Defined as the ratio of the number of animals producing viable litters divided by the number of mice ever pregnant.

(c) Numbers are mean ± S.D.; Group size is indicated in parenthesis; Significance is given as alpha level, or as not significant (N.S.).

(d) One animal in the vehicle control group was unaccounted for after day 18.

Table 70. Ethylene glycol monoethyl ether (EGEE): Litter Data

	Vehicle Control deionized H2O	Test dose 3605 mg/kg
No. viable litters (n)	31	0
No. stillborn litters	0	0
Live pups per litter within 12 h. postpartum	10.1 ± 2.8	-
Dead pups per litter within 12 h. postpartum	0.1 ± 0.4	-
% dead pups/litter within 12 h. postpartum[a]	[0.9 ± 0.9]	-
Live pups per litter on day 3 postpartum	10.1 ± 2.8	-
% pup viability per litter (days 1-3)[b]	[10.1 ± 0.1]	-
Litter wt. on day 1 postpartum (g)	16.1 ± 3.7	-
Litter wt. on day 3 postpartum (g)	20.3 ± 4.3	-
Change in litter weight between days 1-3 (g)	4.2 ± 1.1	-
% Change in litter weight between days 1-3[c]	[5.1 ± 0.7]	-

(a) $\bar{x}$, SD, and ANOVA after $\sqrt{r + 0.5}$ data transformation, where r = % deaths/litter. [ ] indicates transformed data.

(b) % change in litter weight = (Wt. (day 3) - Wt. (day 1) / Wt. (day 1) x 100. $\bar{x}$, SD, and ANOVA, after $\sqrt{r}$ data transformation, where r = % change in litter weight. [ ] indicates transformed data.

(c) % change in litter weight = (Wt. (day 3) - Wt. (day 1) / Wt. (day 1) x 100. $\bar{x}$, SD, and ANOVA, after $\sqrt{r}$ data transformation, where r = % change in litter weight. [ ] indicates transformed data.

5.0 DISCUSSION AND CONCLUSIONS

Nine NIOSH compounds were tested in the mouse modified postnatal screening assay for reproductive toxicity. This test (Chernoff and Kavlock, Teratology 21 (2):33A, 1980) is used to identify and prioritize chemicals in need of further reproductive toxicology testing. This method screens chemicals for embryonic, fetal and neonatal toxic responses, using daily treatment of pregnant mice during the period of major embryonic organogenesis with a previously determined maximum tolerated dose level.

Sodium selenite and toluene cause no significant reproductive toxicity at their designated maximum tolerated doses by these tests.

Ethylene thiourea caused significantly reduced numbers of live pups per litter within 12 hours post-partum and at 3 days post-partum. Whether fewer live births actually occurred, or there was cannibalization of live pups by the mother, this is still a significant effect.

Ethylene glycol monobutyl ether and 2,4-dinitrotoluene cause substantial numbers of resorptions and maternal deaths, and therefore reduce the reproductive index markedly. Weights of mothers and offspring, and the viability of litters which are carried to term, however are not significantly affected.

Diethylene glycol monomethyl ether and 2,4-diaminotoluene also cause substantial numbers of resorptions and maternal deaths, but also substantial numbers of stillbirths, and a greatly reduced reproductive index. Statistical analyses of data for reproductive toxicity in mothers and litters were highly significant.

Ethylene glycol monomethyl ether and ethylene glycol monoethyl ether caused extreme reproductive toxicity. No viable litters were born to mated females dosed with the designated maximum tolerated dose of these chemicals at all. All pregnancies of surviving mothers were resorbed *in utero*.

4.2 Ethylene thiourea (EtTu)

Significantly fewer live pups per litter were present both 12 hours after birth and 3 days postpartum in mated females tested with this chemical. Other measures of reproductive toxicity were not significantly affected. However, the trend towards greater percentage dead pups per litter within twelve hours of birth may be noted. The same additional comments with regard to the births prior to weighing on day 18 due to inappropriate designation of "day 1" apply to this test as for the previous chemical. The statistics were handled similarly for both test and control groups.

4.3 Diethylene glycol monomethyl ether (DGME)

Five mated female mice of the fifty, which were administered this chemical at the designated tolerated dose, died during the dosing period. At necropsy, none were found to have evidence of gavage error; four were pregnant when they died. Eighteen of the remainder resorbed their litters in utero. Nine litters were stillborn. Only five managed to produce viable litters, out of the group mated, yielding a very low reproductive index (0.14). During the subsequent three days another litter died out entirely. The live pups uniformly did more poorly than did the live pups in the control group. Where there was sufficient data to support effective statistical analysis (all measures except number of dead pups within 12 hours), highly statistically significant differences were found between test and control groups for all other measures of reproductive toxicity.

4.4 Ethylene glycol monomethyl ether (EGME)

Seven mated female mice died, of the fifty dosed with this chemical, and only one death could be attributed to gavage error. All 7 were pregnant, and two of these pregnancies were resorbed. Every one of the remaining (30) pregnant mice resorbed their litters in utero. There were no viable births, and no litters even carried to term. No statistical manipulations were necessary, therefore, to conclude that this material is highly toxic to the normal reproductive process at all stages except the earliest ones of fertilization and implantation. The reproductive index was 0.00, due to uniform failure of gestational completion, and the deaths of all fetuses in utero.

4.5 Ethylene glycol monoethyl ether (EGEE)

Five mated female mice died in the test group (two during the dosing period and three after the dosing period was completed), and three of these five were pregnant. No deaths could be attributed to gavage error. All of the (32) remaining pregnant mice resorbed their litters in utero. No viable births occurred, and the reproductive index was 0.00. Due to the highly feto-toxic nature of these effects, to all reproductive phases subsequent to implantation, no statistical analysis is required for its demonstration. The toxic effects of this and the previous chemical on the reproductive process appear similar, by the measures tested in these experiments.

4.6 Ethylene glycol monobutyl ether (EGBE)

Eleven mated female mice dosed with this chemical died; four during the dosing period, and seven after dosing was completed. None of the deaths were due to gavage error. Five of these eleven were pregnant. One of these pregnant mice gave birth and died subsequently. The difference between the test and control groups in the number of viable litters produced is a reflection of both the direct toxicity of the chemical, and also its reproductive effects, i.e., that of causing in utero deaths. The difference in the reproductive index is markedly affected by the seven resorbed litters in the test group. No other statistical measures of reproductive toxicity were significantly different between test and control groups. However, the trend toward lower maternal body weight gains during pregnancy and lower maternal body weights at term, may be noted.

4.7 Toluene (TOL)

Only one test animal died during the experiment and there were no statistically significant differences between test and control groups in any of the categories for evaluation of reproductive toxicity. A nonsignificant trend towards lower weight gain in pregnancy may be noted.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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Associate Director, Product Safety
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Danbury, Connecticut 06817-0001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAY 0 8 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and **refer to the reverse side of this page for "EPA Information Requests"** .

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12449A

Triage of 8(e) Submissions

Date sent to triage: 12/14/95

NON-CAP (CAP)

Submission number: 12449 A

TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI (RTOX) GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: (0) 1 2 **pages** 1, 2 **pages** 1, 2, 4, 5, tab

Notes:

Contractor reviewer : KPS **Date:** 4/14/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-0992-12449 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Union Carbide Corporation

SUB. DATE: 09/24/92 OTS DATE: 09/29/92 CSRAD DATE: 02/02/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0539) REFER TO CHEMICAL SCREENING
(0575) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/INITIATED
0403 NOTIFICATION OF WORKER/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
110-80-5
96-45-7
111-76-2
109-86-4
108-88-3

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA: NON-CBI INVENTORY
(YES)
CAS SR NO
DE MINIMIS

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
mus

TOXICOLOGICAL CONCERN:
LOW
MED
HIGH

USE:

PRODUCTION:

COMMENTS

Repro effects in mice of 9 cmpds:
Mouse Modified postnatal screening assay
(Chernoff + Kavlock)

♂(Low) — No significant repro tox w/ sodium selenite + toluene
♂(HIGH) — ↓ #s of live pups/litter w/ Ethylene thiourea
♂♀(HIGH) — Ethylene glycol monobutyl ether, + 2,4-dinitro-toluene ↑ resorptions & maternal deaths
♂♀(HIGH) — Diethylene glycol monomethyl ether + 2,4 diamino toluene ↑ resorptions + maternal deaths
♂♀(HIGH) mono-ethyl ether extreme repro tox ← Ethylene glycol monomethyl ether + ethylene glycol monomethyl